THE EFFECTS OF ISOTRETINOIN ON FOLLICULAR AND SEBACEOUS GLAND DIFFERENTIATION.

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Isotretinoin is known to reduce the rate of sebum secretion and to shrink sebaceous glands. How these effects are caused and whether the response in acne also depends on an effect on follicular keratinisation is unknown.

Non-lesional skin from the acne bearing area of the back from 17 acne patients was examined at 4 or 8 weeks of isotretinoin treatment. Glucose-6-phosphate dehydrogenase (G6PDH), succinic dehydrogenase (SDH) and non specific esterase (NSE) reaction products were measured in interfollicular epidermis, follicular and sebaceous epithelium, as indices of metabolic activity. Protein synthesis was assessed by a quantitative autoradiogic method using tritiated leucine. The volumes of sebaceous gland, differentiated and undifferentiated sebaceous epithelium and follicular epithelium were measured by a stereological point counting technique. Sebaceous gland cell size and hair follicle orifice area were also measured.

There was a significant reduction in the reaction products of G6PDH and SDH activities in sebaceous glands but no change in interfollicular or follicular epithelium after treatment. No change in protein synthesis could be detected. There was a significant decrease in the volume of sebaceous glands and differentiated sebaceous epithelial cells. The ratio of differentiated to undifferentiated sebaceous cells fell significantly during treatment. There was no change in the volume of the hair follicle or follicular epithelium or in the hair follicle orifice area.

The results confirm that isotretinoin reduces sebaceous gland volume and demonstrate that the glands also have a reduced metabolic activity after isotretinoin treatment. No change in follicular epithelial differentiation was detected by the methods used. Etretinate has been shown to alter the metabolic activity in interfollicular epidermis, indicating one difference in the mode of action of these two retinoids.

A NEW CHEMICALLY STABLE RADIO-LIGAND (CD270) AND ASSAY PROCEDURE FOR CYTOSOLIC RETINOIC ACID BINDING PROTEIN.

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The biological and therapeutic activity of retinoids is believed to be related to their ability to bind to a cytosolic protein receptor - cytosolic retinoic acid binding protein (cRABP), which participates in the nuclear translocation of the retinoid. Until now, [^{3}H]-retinoic acid has been used to measure the binding and to quantitate the amount of cRABP in cell (or tissue) extracts. Retinoic acid (RA), however, is a very unstable molecule, sensitive to light and oxidation. This instability is increased by radiolysis, and in spite of the precautions taken, breakdown of RA is an ever-present problem.

We have developed a new retinoid that can successfully substitute for retinoic acid as a ligand for cRABP. The new retinoid, 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtyl)-6-benzo-[b]-thiophenecarboxylic acid, coded CD270, is labelled specifically with tritium on the naphthalene moiety and has a specific activity of 7.6 Cymmol. This retinoid is chemically stable and insensitive to light or atmospheric oxidation.

At the same time, a new assay procedure has been developed to measure the binding to cRABP. The method allows a complete separation between the bound and free retinoid by means of gel-filtration on small columns of Sephadex G-25. A single fraction (of the cRABP-retinoid complex) is collected from each column into a scintillation counting vial. A single person can run 60-100 samples per day (4-6 binding curves). This assay is used to measure the binding in either saturation- or competition binding experiments. CD270 binds to cRABP from several sources (human, rat, mouse, bovine) with affinity similar to that of RA (K_d of about 2 nM for both). When measuring the affinities of unlabelled retinoids by competition binding, the results obtained were the same irrespective of whether RA or CD270 was used as the radioactive ligand. When cRABP was quantified in human epidermal keratinocytes and in cytosol from rat and bovine testes, again the results obtained with CD270 were similar to these obtained with RA.

These experiments confirm that CD270 binds to cRABP with an affinity and specificity similar to those of RA. We propose therefore, [^{3}H]-CD270 as a chemically stable ligand for cRABP, that can successfully substitute for RA in most binding studies.

A NEW METHOD TO STUDY PRURITUS AND ANTIPRURITIC DRUGS

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A major obstacle in the study of clinical itch and its therapeutic control, is the lack of accurate methods for its measurement. In this study we have used a new method based on a micro-computer (Pain-Track®) in an attempt to increase reliability and compliance of subjective ratings of pruritus. Pain-Track is a portable data logger (8.5x14x2.5 cm; 300 g). With a standard battery of 9.5 V, a continuous recording for at least 8 weeks can be made. Every 60 min a buzzer commands the patient to mark his presence on a marker button and rate the itch intensity on a knob with a fixed point scale from 0 to 6 (0=no and 6=maximal itch). During nighttime the hourly buzzer can be turned off, but the intensity rate knob can still be changed whenever wanted. When the recordings are finished the data logger is plugged into a desk-top computer for storage and analysis of the collected information.

In a double-blind, cross-over study 30 adult out-patients with persistent atopic dermatitis were treated with betamethason dipropionate or its corresponding cream base. We measured the itch intensity during each period (6 days) of treatment, both continuously by Pain-Track and retrospectively each day by conventional diary cards. The overall compliance with Pain-Track was 90%. In 19 of the 20 pts who had a compliance rate of >80% the itch intensity measured by Pain-Track was less during active treatment than during placebo. In many cases the decreased itch was recorded already during the first day of treatment. Moreover, there was a good correlation between the clinical picture and itch intensity.

Conclusion: By using a drug with known antipruritic effect in atopic dermatitis we have shown that Pain-Track is a useful tool for assessing clinical pruritus and the antipruritic effects of drugs. The main advantages of the new method are possibilities for: 1) frequent recordings, 2) surveillance of compliance, 3) storage and analysis of a large amount of data.

Calcium Channel Antagonists in Dermatology

Smooth muscle contraction is calcium dependent. Calcium influx into the smooth muscle cell can be blocked by a group of drugs which block the 'slow' calcium channels. Of these drugs nifedipine, verapamil and diltiazem have powerful effects on both the coronary and peripheral vasculature - hence their use in cutaneous disorders in the aetiology of which vascular or smooth muscle spasm are implicated.

Nifedipine has been most extensively used in Raynaud's phenomenon. It must now be accepted as a first-line drug in the management of severe symptomatic Raynaud's phenomenon, providing symptomatic relief in approximately 60% of patients. In resistant patients its use in combination with prostacyclin analogues can result in symptomatic relief and improvement of cutaneous blood flow.

Severe chronic idiopathic pernionis has hitherto been resistant to therapy but recently nifedipine (modal dose 60 mg orally daily) has been demonstrated to relieve symptoms, promote healing and prevent occurrence of further lesions in approximately 70% of patients with previously unremitting disease.

The severe pain of leiomyomata has also been relieved by nifedipine in a small number of patients and its use in this disorder merits further investigation.

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IMPROVEMENT AND VALIDATION OF IN-VITRO METHODS FOR ROUTINE TESTING IN DERMATO-TOXICOLOGY.

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The use of animals in biological experiments as well as in dermato-toxicological investigations worldwide has become an issue of intensive public discussion. In contrast to an increasing number of papers on new alternative methods for RRR (Refinement, Reducement, Replacement) of animal experiments, there is a lack of in-vitro systems which have been validated sufficiently to justify their use in routine testing. Based upon recent work in our own laboratory and on previous papers by other authors three in-vitro systems of different complexity were selected for standardization and validation in a two year collaborative study, sponsored by the Federal Ministry for Research and Technology: a) cell culture, b) skin culture, c) chorion allantoic membrane (CAM) of incubated hen's eggs. All these systems proved to be suitable for routine testing. Cell and skin cultures provide good results when used for comparative testing within the same class of chemicals. But both methods have limitations with respect to chemical and physical properties of the products and chemicals to be tested. Best results were obtained with the chorioallantoic membrane. As this system seems most appropriate for further standardization with the aim to replace animal tests for skin and eye irritancy, further studies on improvement of evaluation methods and on defining a system of validation chemicals are performed presently. It is obvious, that no in-vitro system can be expected to meet all requirements of all different problems. But for a lot of aspects of testing for local effects there is a good chance to replace animal tests by CAM-testing in the near future.

INTERFERONS IN DERMATOLOGY. G. Mahrle, H.-J. Schulze, H. Rassfeld, B. Thiele, H.F. Merk, Dept. of Dermatology, University of Cologne, West Germany.

Interferons (IFN) modulate proliferation, differentiation and HLA-DR expression. Clinical studies on the effect of interferons proved some benefit regarding the treatment of viral infections and skin tumors, such as melanoma and basal cell carcinoma.

We report on (1) the effect of rIFN-gamma on growth, differentiation, and AHH activity of cultured keratinocytes and (2) its influence on HLA-DR expression and DNA-synthesis in psoriatic epidermis. We present our results obtained by two clinical trials, (A) phase II/III study on the effect of rIFN-alpha in AIDS and AIDS-related Kaposi's sarcoma (n = 24) and (B) phase I/II study on the effect of rIFN-gamma in 28 patients with melanoma, arthropathic psoriasis, condylomata acuminata, epidermodysplasia verruciformis, bowenoid papulosis, Behcet's disease, and mycosis fungoides.

IFN inhibited cell growth of keratinocytes in vitro but not in vivo in psoriatic epidermis. IFN-gamma induced expression of HLA-DR in keratinocytes in vitro as well as in vivo. rIFN-alpha caused regression of Kaposi's sarcoma in some cases but did not influence immunodeficiency. rIFN-gamma was of some benefit in the treatment of genital warts, bowenoid papulosis, and Behcet's disease but there was no response of psoriasis.

CELL CULTURE MODELS IN SKIN PHARMACOLOGY AND TOXICOLOGY.

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Human cells in culture are being used with increasing frequency as in vitro models for studying toxicological and pharmacological mechanisms at the cellular level. Changes in cellular properties such as the adhesiveness of anchorage-dependent cells to their culture support, cell membrane permeability, respiratory and overall metabolic activity as well as the capacity of the cells to proliferate or differentiate have been monitored under the influence of a given drug by measuring, for example, cell detachment, release of intracellular material (ATP, enzymes, DNA), exclusion of trypan blue or uptake of vital dyes, alterations in gas exchange and heat production as well as thymidine incorporation or the expression of specific differentiation markers.

In the present review the usefulness of the cell culture approach will be discussed by comparing the dose response of transformed human keratinocytes in vitro to different antipsoriatic treatments (anthralin, PUVA, glucocorticoids and retinoids) with data obtained under therapeutic conditions in vivo. The following cellular parameters are taken into consideration: cell detachment, thymidine incorporation, glutamine deamination and cornified envelope competence as measures, respectively, of cytotoxicity, proliferative activity, cellular respiration and the capacity of the cells to undergo terminal differentiation.

The results indicate that, at therapeutic concentrations, anthralin and PUVA exert their antipsoriatic action via their cytotoxic potential by either inhibiting cellular respiration or DNA replication, whereas retinoids and glucocorticoids do not act directly as cytotoxic drugs but rather modulate the equilibrium between epidermal proliferation and differentiation by as yet unknown mechanisms. Furthermore, our data support the view that cell culture systems can provide a useful tool for the screening of new chemical derivatives of certain drugs.

USE OF AIR-EXPOSED KERATINOCYTE CULTURE FOR PHARMACOLOGICAL PURPOSES.

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Using a conventional (submerged) culture system keratinocytes undergo differentiation, although to a degree which is lower than that seen under the in vivo situation. When cultured at the air-liquid interface using dead de-epidermized dermis (DED) as a substrate, keratinocytes were found to express morphological features of differentiation similar to those seen in vivo. Therefore, the latter system offers an attractive model for studying the processes involved in the regulation of epidermal differentiation and the effects of drugs on it.

The analysis of the lipid composition of normal keratinocytes cultured on DED revealed a great similarity of lipid pattern with that seen under the in vivo conditions. In contrast to cells cultured in a submerged culture system, which contain relatively large amounts of phospholipids and low quantities of ceramide, cells cultured on DED contain low amounts of phospholipids and high amount of sterols and ceramides, especially of acylceramides. Under both culture conditions, however, linoleic acid was present in much smaller quantities as compared to the in vivo situation.

Administration of retinoic acid (RA) to both normal and malignant (squamous carcinoma cells (SCC)) keratinocytes induced marked changes in the morphology of cells when cultured on DED. In normal keratinocytes the administration of RA led to an increase of a number of cell layers accompanied by a loss of the granular layer. Furthermore, the horny layer was transformed to a parakeratotic layer and also keratinization of individual cells was observed. In contrast to normal keratinocytes the addition of RA markedly reduced the number of cell layers of all three SCC studied. The morphology of these cells, however, was not significantly altered. These results suggest that similarly to the in vivo situation RA exerts distinctively different effects on the proliferation and differentiation of normal keratinocytes as compared to SCC cells.

COMPARATIVE TOXICITY OF ANTIMICROBIAL AGENTS ON TRANSFORMED HUMAN KERATINOCYTES

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Experimental data suggest that some antimicrobial agents may have an adverse effect on several aspects of the tissue repair process including retardation of wound epithelialization. The aim of this study was to investigate the comparative cytotoxic effects of a range of antiseptics and antibiotics using human keratinocytes transformed by Simian virus 40 (SVK14 cells).

SVK14 cells were grown to semi-confluence by adding 6×10^4 cells per petri dish. After 48 hours the cells were exposed to serial dilutions of the therapeutic concentrations (in parentheses) of each of the following agents: hydrogen peroxide (3%), cetrimide (1%), sodium hypochlorite (0.5%), povidone iodine (4%), neomycin (1%), bacitracin (50 units/ml), polymyxin B sulphate (10,000 units/ml). The cells were exposed to the drug for 15 minutes and then washed and incubated in the culture medium (RPMI 1640 plus 10% fetal calf serum) for 24 hours. Dead cells were then washed off and the viable adherent cells were trypsinised and counted in a Coulter counter.

At therapeutic concentrations none of the antibiotics were found to be cytotoxic whereas all of the antiseptics produced 100% killing of SVK14 cells. Dilutions of therapeutic concentrations of the antiseptics ranging between 1000- and 20,000-fold (depending on the agent) were needed in order to achieve no-effect levels. Calculations based on 100% killing values for the antiseptics indicate that their order of toxicity from highest to lowest is sodium hypochlorite, cetrimide, povidone iodine and hydrogen peroxide.

We conclude that this cell line may be useful in studying the epithelial cytotoxicity of drugs in vitro and that care should be exercised in the selection of antimicrobial agents for use in wound management.

INFLUENCE OF DERMAL FIBROBLASTS ON EPIDERMALIZATION

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We recently describe a method of epidermalization in vitro that permits to obtain a well differentiated human epidermis and to quantify this epidermalization (1). With this human living skin equivalent model, composed as in vivo of a dermis and an epidermis, we could demonstrate that fibroblasts from psoriatic patients induce the hyperproliferation of normal keratinocytes (2). In this study, we investigated the influence of normal dermal fibroblasts on epidermalization.

Normal human dermal fibroblasts are combined with collagen, serum and culture medium. Almost immediately a gel forms which the fibroblasts begin to contract. Within a few days, the contraction is stabilized and a tissue of firm consistency is formed : the dermal equivalent (DE) (3). In this three dimensional collagen matrix, fibroblasts are in a state of differentiation similar to that observed in vivo, (4). At different steps of the rearrangement of the collagen matrix by fibroblasts, cells are killed by an osmotic shock. So, matrices of different consistency can be made, in which fibroblasts can be alive or dead. Epidermalization is then initialized by seeding on these matrices either very thin (mm in diameter skin punch biopsies (epidermis and superficial dermis) or 2 mm in diameter biopsies made in suction blister roof (Epidermis alone).

The epidermalization is better on a collagen matrix that have been previously reorganized by the fibroblasts, than on a simple collagen gel.

The presence of the fibroblasts of the biopsy promotes the epidermalization when no living fibroblasts are in the DE, but this effect is masked when fibroblasts are alive in the DE.

For a same collagen texture, the epidermalization is promoted when the fibroblasts of the dermal equivalent are alive.

Thus fibroblasts influence the epidermalization, they not only remodel the extracellular matrix, but also secrete growth factors. These results underline the importance of the fibroblasts in the dermal-epidermal interactions and the living skin equivalent provide to study these interactions. Because this human skin equivalent can be made simple or complex, the effects of pharmacological agents on epidermalization can be evaluated in this culture model either by their actions on keratinocytes themselves or through the treatment of the dermal fibroblasts.

(1) Coulomb et al. Br. J. of Dermatol., 114, 91-101, (1986). (2) Saing et al. Science, 230: 669-672, (1985). (3) Bell et al. Proc. Natl. Acad. Sci. USA, 76 : 1274-1278, (1979). (4) Coulomb et al. Br. J. of Dermatol., 111, suppl. 27, 83-87, (1984).

1,25 DIHYDROXYVITAMIN D_3 METABOLISM AND RECEPTOR CONTENT IN CULTURED HUMAN EPIDERMAL KERATINOCYTES AS A FUNCTION OF DIFFERENTIATION.

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Human foreskin keratinocytes produce 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) in a hormonally-regulated fashion and contain receptors for $1,25(OH)_2D$. Here, we investigated how $1,25(OH)_2D_3$ production and $1,25(OH)_2D$ receptor content is linked to epidermal differentiation using cultured neonatal foreskin keratinocytes. At different stages of confluence, cells were serum-deprived for 24 hrs, and examined for production of $1,25(OH)_2D$ or $24,25(OH)_2D$ from ^3H-$25(OH)D$, receptor content and affinity, and differentiation markers (transglutaminase (TG), involucrin (I), and cornified envelope (CE)). Whereby maximal production of $1,25(OH)_2D$ occurred after the cultures reached confluence, the highest specific activity of 1-α-hydroxylase occurred just before confluence, when the cells also began to express TG, I, and CE activities. In post-confluent, fully-differentiated cultures $1,25(OH)_2D$ production declined dramatically along with TG and I as $24,25(OH)_2D$ production increased. Keratinocyte cytosols, prepared by high-speed centrifugation from pre-confluent, confluent and post-confluent keratinocytes, and examined for $1,25(OH)_2D$ receptors by equilibrium binding and sucrose gradient centrifugation, possessed receptors of the same sedimentation characteristics as chick intestinal cytosol preparations. Scatchard analysis displayed a single class of binding sites at all stages of growth, with pre-confluent cells displaying the highest receptor concentration (35 fmol/mg protein) of high affinity (kd-270 pM), confluent cells showing less (25 fmol/mg protein) of high-affinity receptors, and post-confluent cells displaying lower numbers (25 fmol/mg protein) of low-affinity receptors (kd-1400 pM). The correlation of $1,25(OH)_2D$ production and receptor content with keratinocyte differentiation markers supports a regulatory role for vitamin D metabolites in epidermal differentiation.

A COMPARATIVE STUDY OF THE EFFECTS OF NSAIDs, CORTICOSTEROIDS, RETINOIDS AND ANTHRALIN ON HUMAN PMN MIGRATION, OXIDATIVE BURST, DEGRANULATION AND 5 LIPOXYGENASE ACTIVITY

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The acute inflammatory component of various skin disorders, e.g. psoriasis, is characterized by a pronounced invasion of the skin with PMNs. Using human neutrophils, the influence of drugs with potential interest to dermatology was studied in vitro, in order to delineate their action spectrum on cellular activities of possible relevance to cutaneous inflammation: PMN migration (random and directed), lysosomal enzyme release and active oxygen production as well as 5-lipoxygenase activity. The cells were continuously incubated with the drugs when migration (chemokinesis and chemotaxis) stimulated by the chemotactic peptide FMLP was studied, whereas a short (15 min) treatment of the cells preceded the assessment of cellular responsiveness to FMLP (oxidative burst, degranulation) or A23187 (5-lipoxygenase). Cellular movement was depressed by micromolar concentrations of most drugs including retinoids, the strongest inhibitors being Indomethacin, Phenylbutazone, BW755C, Retinoic acid, Arotinoid and Anthralin. In contrast, 5-lipoxygenase activity remained unaffected after treatment by virtually all agents except known lipoxygenase inhibitors (Caffeic acid, NDGA, BW755C, ETYA, Benoxaprofen) and was marginally affected by large concentrations of Retinoic acid and Arotinoid. The oxidative burst as measured by chemiluminescence in the presence of Luminol, and degranulation, as quantified by the release of lysozyme, were inhibited by some but not all cyclooxygenase inhibitors (e.g. Indomethacin, Phenylbutazone). Lipoxygenase inhibitors and retinoids (Arotinoid) were potent antagonists of active oxygen production. In the cases of Caffeic acid and BW755C, these effects could at least partially be explained by antioxidant properties of the molecules since similar observations could be obtained in a cell free O_2^--producing system. Degranulation was usually less sensitive to these drugs, retinoids being totally ineffective. Anthralin consistently gave bimodal dose-response curves in the chemiluminescence assay (mild stimulation at [illegible] M, partial inhibition at 10^{-5} M), and a slight stimulation of degranulation. Under these experimental conditions (short duration incubations), corticosteroids were almost devoid of any inhibitory activity. Taken together, these results show that depression of PMN migration and production of oxidants are the most common targets of the drugs investigated and could be part of their mode of action.

EFFECTS OF LIPOXYGENASE-DERIVED EICOSANOIDS ON FIBROBLASTS: CHEMOTACTIC ACTIVITY AND REGULATION OF COLLAGEN SYNTHESIS.

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Metabolism of fibroblasts (fb) plays an important role in wound healing and can be modulated by other cell types. In a search for soluble molecular signals produced by these cells, we investigated the effects of eicosanoids on fb function. Chemotactic activity of fb was assessed in a blind well Boyden chamber with various eicosanoids as chemoattractants. Fb proliferation was measured by cell counts, and their biosynthetic capacities by 3H-proline labelling. For measuring the synthesis of collagen and non-collagenous proteins, the newly synthesized material was dialyzed, hydrolyzed and analyzed on an automated amino acid analyzer.

LTB4, 5S- and 12S-HETE were found to be strongly chemotactic for fibroblasts. Structure-activity analysis revealed that the position of hydroxylation on C5 and C12 was essential for chemotactic activity. Preincubation of cells with 12S-HETE reduced the chemotactic response to 5S-HETE and LTB4, indicating that these eicosanoids utilize the same cell surface receptor, whereas chemotaxis to other chemoattractants such as fibronectin and PDGF was unaffected by 12-HETE. Total protein synthesis was not influenced by any of the eicosanoids tested, however, a specific decrease of collagen synthesis was noted in the presence of 12S-HETE.

These results suggest a possible role of eicosanoids in the regulation of fb metabolism during chronic inflammation and in fibrotic processes. Of particular interest is the activity of 12-HETE, the main product of arachidonic acid in epidermis with unknown function, which may serve as a molecular signal between epidermis and dermis.

ARACHIDONIC ACID INDUCED EAR OEDEMA IN THREE STRAINS OF RATS AND MICE: A COMPARATIVE STUDY OF ANTI-INFLAMMATORY DRUGS.

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Topical application of arachidonic acid (AA) to the mouse ear induces an inflammatory response associated with the formation of prostaglandins and leucotrienes (CHANG et al, 1986, Inflammation 10, 205-214).

We now report a comparison of the inhibitory responses of three strains of rats (OFA, WISTAR, Hairless) and mice (CD1, C3H, NMRI) to a variety of known anti-inflammatory agents. Oedema responses were measured either at 4 h or 2 h post topical arachidonic acid application, which had previously been found to provoke maximum oedema formation in mice and rats respectively.

Indomethacin, BW755, 5,8,11,14-ETYA were active in all the strains of both rats and mice. Naproxen was less active in mice. Hydrocortisone was inactive in all of the animals tested. Whilst both Betamethasone-17-valerate and Nordihydroguaiaretic Acid were inactive in the different rat strains they were none the less active in the mice strains. The different inhibitory effects obtained for the same anti-inflammatory agent in different animals and strains of animals is probably attributable to a variety of reasons including different end organ effects and pharmacokinetic influences.

These results confirm the need of careful choice in the selection of suitable animals and strains when developping animal models for topically applied drugs.

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